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Genotypic and phenotypic relationship between Prader-Willi and Prader-Willi-Like syndromes

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ABSTRACT. Prader-Willi-Like syndrome (PWLS) is a rare genetic disorder with clinical features that include hypotonia, obesity, short extremities, and developmental delay. As its name suggests, the clinical phenotypes of PWLS overlap with the genetic imprinting disorder of Prader-Willi Syndrome (PWS). The sharing of phenotypes between these syndromes likely indicates that the genomic regions affected in PWLS are involved in the same genetic pathways associated with developing the PWS phenotype. Thus, the genetic heterogeneity of PWLS and the absence of a molecular diagnosis associated with PWS constitute a clinical challenge for health professionals. This review presents phenotypic and genotypic characteristics related to PWLS described in 34 articles, totaling 74 patients, including alterations involving deletion of 1p, 2p, 6q, 15p, duplication of 15q, Xq, Temple Syndrome, Schaaf-Yang Syndrome, Fragile X syndrome, and even associated mutations. Among the most frequent characteristics related to PWLS are global developmental delay (78%), obesity (68%), hypotonia (51%), speech-articulation problems (42%), and behavioral disorders (41%). This review provides an overview of current knowledge of the genetics and phenotypes associated with PWS and PWLS.

Key words: Prader-Willi syndrome; Prader-Willi-Like syndrome; Obesity; Imprinting disorder; Mental deficiency

INTRODUCTION

Prader Willi-Like syndrome (PWLS) is a rare disorder whose clinical features include hypotonia, obesity, short extremities, and developmental delay (1). PWLS shares features with Prader-Willi Syndrome (PWS), and different genetic mechanisms cause this overlap of phenotypes. The clinical overlap between the two syndromes makes accurate diagnosis difficult, and correct diagnosis can aid in proper management and provide conclusive genetic explanations and accurate genetic counseling.

The mechanisms that lead to PWLS have not yet been elucidated. However, it is believed to involve disruptions in various genetic pathways throughout the genome. For example, PWLS does not show any alteration in the 15q11-q13 region (Berends et al., 1999). Some cases were reported in which patients presented the phenotype described as PWS but without alteration in the specific region. For example, an investigation of these patients showed changes involving the 1p, 2p, 3p, 6q, and 9q regions, Temple Syndrome, Fragile X Syndrome, and Schaaf-Yang Syndrome (Berends et al., 2009; Cheon, 2006; Schaaf et al., 2013; Angulo et al., 2015). This work examines the most frequent phenotypic characteristics associated with the different genotypes related to PWLS to facilitate the diagnostic process.

MATERIAL AND METHODS

This article is a literature review of case reports of individuals who had the phenotype related to PWLS, intending to obtain a descriptive panel, relating genotypes and phenotypes and observing the frequency of phenotypic characteristics. The search was carried out in April 2022, using the search platform "National Center for Biotechnology Information" (www.pubmed.com), with the search engine ("Prader-Willi-Like"[All Fields] AND ("syndrome "[All Fields] OR "syndromal"[All Fields] OR "syndromal"[All Fields] OR "syndrome"[MeSH Terms] OR "syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s" [All Fields] OR "syndromic"[All Fields] OR "syndrome"[All Fields])"). The terms were combined using "OR" and "AND" logic. Forty-nine articles were found, with no duplications. As inclusion criteria, articles were considered with individual case descriptions, regardless of the publication date, excluding bibliographic reviews, protocols, letters, and editorials (Figure 1). The 34 articles that met the criteria were included in the review: age, gender, genotype, and clinical characteristics.

The survey of the clinical profile of the patients was carried out based on the methodology described by McCandless SE; Genetics Committee 2011 (McCandless, 2011) (Supplementary Material 1). Phenotypic features not described as PWS and the frequency of patients are listed in Supplementary Material 2.

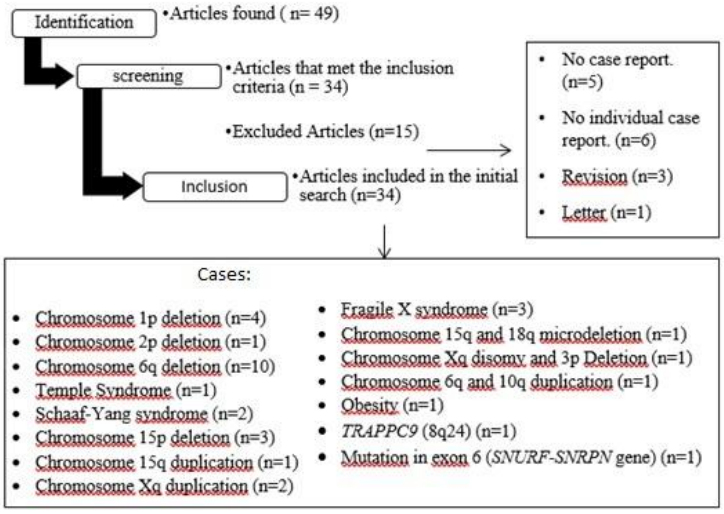

Figure 1. Diagram with the summary of the literature review search used for Prader-Willi-Like Syndrome

RESULTS

We found 49 articles related to PWLS, with 34 articles from the United States: 9, France: 4, Holland: 4, Italy: 4, Brazil: 3, Japan: 2, Belgium: 1, Canada: 1, China: 1, Colombia: 1, Spain: 1, Estonia: 1, Sweden: 1, Tunisia: 1, met the inclusion criteria. Within the analyzed articles, 74 patients were reported, 45 males and 29 females (Table 1).

Table 1. Summary of genotypes described in articles as related to Prader-Willi-Like Syndrome.

Genotype	1p del	2p del	6q del	Temple SYN	Schaaf-Yang SYN	15q del	15q dup	Xq dup	X fragile SYN	15q Micro del + 18q Microdup	Xq disomy + 3p del	6q dup + 10p dup	Obesity	TRAPPC9 (8q24)	Mut in SNURF-SNRPN
Number of papers	4	1	10	1	2	3	1	2	3	1	1	1	1	1	1
Number of cases	9	5	29	1	4	3	3	2	10	1	1	1	2	2	1
Gender (M/F)	2/7	¼	21/8	0/1	1/3	2/1	2/1	1/1	10/0	1/0	1/0	1/0	2/0	0/2	0/1

Note: del: deletion, SYN: syndrome, dup: duplication and Mut: mutation.

The age group of 5 infants, 7 preschoolers, 27 schoolchildren, 22 adolescents, 11 young adults, and two adults, taking into account the date of the last day of follow-up until the publication of the articles (Figure 2), among which they presented the following genetic causes.

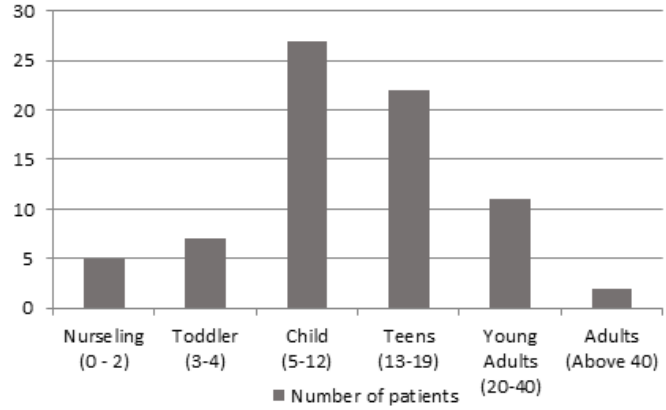

Figure 2. Graph showing the age of Prader-Willi-Like Syndrome patients when they were reported.

Chromosome 1p Deletion

There were nine patients described with 1p deletion, which was reported as follows: Tsuyusaki et al (Tsuyusaki et al., 2010), and Stage et al (2014). 2 cases each, which involved the D1Z2 gene; Oiglane-Shlik et al. (2014), 4 cases with a deletion in the KLHL17, PEX10 and GABRD genes; D'Angelo et al. (2006) 1 case with a deletion close to the PEX10 gene.

Phenotypic characteristics related to PWS were: Global developmental delay- 7, short stature- 2, small-appearing mouth/thin upper lip- 3, weak or high-pitched cry in infancy- 1, clinodactyly- 3, seizures- 3, diabetes mellitus (type 2)- 2, learning disability- 2, behavioral disorders- 4, scoliosis- 1, strabismus- 5, palpebral fissures- 2, hyperphagia- 6, hyperinsulinemia- 2, hypopigmentation- 2, hypotonia- 9, little hands with straight ulnar border- 1, small hands- 2, myopia- 2, obesity- 4, small feet- 3, speech-articulation problems- 6, weak neonatal sucking and swallowing reflexes- 3, gastroesophageal reflux- 1, excessive daytime sleepiness- 1 and excoriation disorder- 2 (D'Angelo et al., 2006; Tsuyusaki et al., 2010; Õiglane-Shlik et al., 2014; Stage et al., 2014).

Among the other characteristics are: Overweight- 1, isolated coccygeal bone agenesis- 1, brain anatomical alterations- 3, oral aspiration- 1, astigmatism- 1, slow and/or low background activity- 1, increased blood copper- 1, lack of independent gait- 1, brachycephaly- 2, cataract- 1, cyanosis- 2, tonic-clonic crisis- 1, short toes- 3, atrial septaldefect- 1, spinal deformity- 1, dilation of brain ventricles- 1, epicanthus- 2, capital femoral epiphysiolysis- 1, freezing episodes accompanied with masticatory movements-1, spasms- 1, spasticity- 1, bitemporal narrowing- 1, rounded face/full cheeks- 1, dysmorphic phenotype- 1, large/open anterior fontanelle- 1, weight gain between 1 and 6 years- 1, hemagioma- 1, hyperactivity- 1, hypercholesterolemia- 1, T2 and/or FLAIR hyperintensity- 4, hypertension- 2, pulmonary hypertension- 1, hypertrichosis- 1, midface hypoplasia- 2, respiratory infection- 1, neurological lesions- 1, sleep myoclonus- 1, microbrachycephaly - 1, microcephaly- 2, late myelination- 1, thyroid nodule- 1, sunken eyes- 6, dysplastic ears- 3, posteriorly rotated ears- 1, small ears- 2, arched/high/huddled palate- 2, facial nerve palsy- 1, general passivity- 1, partial or complete hearing loss- 3 , patent ductus arteriosus- 1, pylorospasm- 1, wide nasal bridge- 2, palmar creases- 1, small chin- 2,

pointed/protruding chin- 2, wide and flat nasal root- 1, exaggerated deep tendon reflexes- 3, regurgitation- 1, insulin resistance- 2, mental retardation- 3, Babinski sign- 2, synophris- 1, bushy eyebrows- 1, straight and/or thin eyebrows- 4, telangiectasia- 1, high and/or prominent forehead- 3, toe walking- 1, impaired glucose tolerance- 1, attention deficit disorder- 1, and benign tumor- 1 (D'Angelo et al., 2006; Tsuyusaki et al., 2010; Õiglane-Shlik et al., 2014; Stage et al., 2014).

Chromosome 2p Deletion

Five patients described by Doco-Frenzy et al. (2014) presented this alteration, having the genes *FAM110C*, *SHY3YL1*, *ACP1*, *FAM150B*, *TMEM18*, *C2ORF90*, *SNTG2*, *TPO*, *PXDN*, and partial deletion of *MYT1L* involved. PWS-related phenotypic characteristics were: obstructive sleep apnea- 2, global developmental delay- 4, small-appearing mouth/thin upper lip- 3, clinodactyly- 2, seizures- 2, learning disability- 4, difficulty gaining weight- 1, behavioral disorders- 2, scoliosis- 1, strabismus- 3, palpebral fissures- 3, hyperphagia- 4, hyperopia- 1, hypotonia- 1, small hands- 2, obesity- 4, small feet- 2, speech-articulation problems- 4 and excoriation disorder -1 (Doco-Frenzy et al. 2014).

Among the other characteristics are: Overweight- 1, ophthalmic pigmentary changes - 1, anxiety- 1, flexible joints- 4, cognitive delay- 1, head shaking- 1, brachycephaly- 1, crying and/or unexplained laughter- 1, short columella- 2, labial commissure- 1, seizures/epilepsy- 1, nasal bridge depression- 3, dyspraxia- 1, epicanthus- 2, stereotypies- 2, rounded face/full cheeks- 1, asymmetrical face- 1, short philtrum- 1, prominent philtrum- 1, weight gain between 1 and 6 years- 3, genu valgus -1, hyperactivity- 3, palmar and/or plantar hypersensitivity- 1, hypertelorism- 2, hyperthyroidism- 1, hirsutism- 1, thick lips- 1, high plasma leptin- 1, low hairline- 2, large lobes- 1, skin patches- 1, anteverted nostrils- 2, small nose- 3, ventricular omegaly- 1, large ears- 2, thick ears- 1, small ears- 1, arched/high palate /heavy- 1, mitral valve prolapse- 1, puberty- 1, permanent salivation- 1, straight and/or thin eyebrows- 1, high and/or prominent forehead- 1, stereotyped movement disorder- 1, elevated TSH- 1, and dystrophic nails- 1 (Doco-Frenzy et al. 2014).

Chromosome 6q Deletion

There were 29 patients with a 6q deletion, with Faivre et al. (2002), Varela et al. (2006) and Izumi et al. (2013) reporting one individual with a mutation in the single-minded gene 1 (*SIM1)* gene. Bonaglia et al. (2008) described five patients with alterations in *GRIK2*, *POPDC3*, and *MCHR2*. Candelo et al. (2018) described one individual who had alterations involving all the genes mentioned above, and El Khattabi et al. (2015) described 15 patients, 13 of whom had a mutation in the *SIM1* gene.

PWS-related phenotypic characteristics were: Tooth crowding and malocclusion- 1, reduced fetal activity- 1, global developmental delay- 24, short stature- 4, small-appearing mouth/thin upper lip- 4, downturned corners of mouth- 1, clinodactyly- 2, seizures- 1, cryptorchidism- 2, impaired motor coordination- 2, GH deficiency- 2, narrow bitemporal diameter- 1, learning disability- 17, behavioral disorders- 16, scoliosis- 1, strabismus- 8, palpebral fissures- 6, hyperphagia- 9, hyperopia- 2, hypogonadism- 1, hypotonia- 11, small

hands- 8, myopia- 5, nystagmus- 2, obesity- 22, almond-shaped eyes- 4, small feet- 7, childhood eating problems- 4, food-related behavioral problems- 2, speech problems joint- 7 and weak neonatal sucking and swallowing reflux- 7 (Stein et al., 1996; Faivre et al., 2002; Varela et al., 2006; Bonaglia et al., 2008; Wentzel et al., 2010; Izumi et al., 2013; El Khattabi et al., 2015; Candelo et al.; 2018; Gonsalves and Newbern, 2020).

Among the other characteristics are: Underweight- 1, overweight- 3, adenoids- 1, tall stature (perinatal)- 2, astigmatism- 3, ventricular conduction delay- 1, ventricular enlargement- 1, no bowel control- 1, no axillary hair- 1, no/few pubic hair- 1, autism- 2, poor language development- 2, extended gait base- 3, brachycephaly- 4, brachymetacarpy- 1, brachymetatarsia- 1, tall hair- 1, thin hair- 1, camptodactyly- 1, cataract- 1, prominent nasal columella- 1, seizures/epilepsy- 1, venereal cord- 1, asymmetric skull- 1, stubby fingers- 4, short fingers- 4, short toes- 2, thin fingers- 1, patent ductus arteriosus defect- 1 aTrial septal defect- 3, gonadotropin deficiency- 1, insulin deficiency/signs of insulin deficiency- 1, intellectual disability- 2, elbow deformities- 1, fetal heart rate decelerations- 2, day central betes insipidus- 1, internal capsule dysmorphia- 1, dyspraxia- 1, abdominal distention- 1, sleep disturbance/difficulty sleeping- 5, marked suborbital folds- 1, neuronal ectopia- 1, entropion- 1, nocturnal enuresis- 1, epicanthus- 3, twisted epididymis- 1, scaphocephaly- 2, angle esophoria- 1, spasms- 1, bitemporal narrowing- 1, round face/full cheeks- 18, asymmetrical face- 1, flat face- 1, square face- 1, triangular face- 1, tapered phalanx- 1, short phalanx- 1, lack of attention- 1, lack of interaction social- 2, clumsiness when walking- 2, marked philtrum- 4, prominent philtrum- 2, fistula in the sacral region- 1, large/open anterior fontanelle- 1, weight gain between 1 and 6 years- 8, gynecomastia- 1, inguinal hernia- 1, umbilical hernia- 1, hyperactivity- 3, hypertelorism- 3, hyperthyroidism- 1, choroid plexus hypertrophy- 1, lobe hypoplasia- 1, hypothyroidism- 2, hirsutism- 1, greater than actual bone age- 1, lower than actual bone age- 1, restlessness- 1, adrenal insufficiency- 1, genu valgus- 1, intrauterine growth limitation/retardation- 1, livedo- 1, small lobes- 1, macrocephaly- 9, Arnold-Chiari malformation- 2, kidney malformation- 1, inverted nipples 1, skin spots- 2, short upper limbs- 1, small jaw- 1, megacysts- 1, metatarsus valgus- 1, microcephaly- 4, microphallus- 1, micrognathia- 1, anteverted nostrils- 1, bulbous nose- 7, thin nose- 1, flat occiput- 1, eyes- 1, oligohydramnios- 1, shallow orbits- 1, low ears- 2, ears with small anti-helices- 1, ears with abnormally bent helices- 2, ears with square helix, ears cauliflower- 1, posteriorly rotated ears- 1, large ears- 4, orchidopexy- 1, arched/high/huddled palate- 3, thick upper eyelids- 1, pectus excavatum- 1, dry skin- 1, sparse pubic hair- 1, small for gestational age - 1, partial or total hearing loss- 3, flat feet- 3, big feet- 1, flat feet- 1, clubfoot- 2, valgus feet- 1, pyeloectasis- 1, pyelonephritis- 1, low thumbs- 1, polydipsia- 1, polyuria- 1, high nasal bridge- 1, thin nasal bridge- 1, wide nasal bridge- 4, flat nasal bridge- 1, poor tendon reflexes- 1, palmar creases- 1, redundant foreskin- 1, constipation- 1, zygomatic prominence- 1, suppressed basal prolactin- 1, ptosis- 3, pointed/protruding chin- 1, flat malar region- 1, prominent occipital and/or frontal region- 1, restricted forearm pronation- 1, restricted forearm supination- 1, mental retardation- 2, retrognathia- 1 , syndactyly- 3, synophris- 3, bushy eyebrows- 1, imperceptible eyebrows- 1, straight or thin eyebrows- 2, heart murmur- 2, high and/or prominent forehead- 6, small testes- 2, tetralogy of Fallot- 1, increased nuchal translucency- 1, attention deficit disorder- 1, short trunk- 1, fragile nails- 1, use of non-verbal communication- 1, large ventricles of the corpus callosum- 1 and ventriculomegaly-1 (Stein et al., 1996; Faivre et al., 2002; Varela et al., 2006; Bonaglia et al., 2008; Wentzel et al.,

2010; Izumi et al., 2013; El Khattabi et al., 2015; Candelo et al.; 2018; Gonsalves and Newbern, 2020).

Temple Syndrome

Balbeur et al. (2016) described one patient who presented maternal uniparental disomy of chromosome 14 (UPD (14) mat), which led to the appearance of clinical features caused by dysregulation of the expression of imprinted genes. Human chromosome 14 carries the imprinted locus 14q32, controlled by the paternal differentially intergenic methylated region (IG-DMR). It contains genes expressed only in the paternal allele (*DLK1*, *DIO3*, and *RTL1*) and genes expressed only in the maternal allele (*GTL2*, *RTL1as*, and *MEG8*). In the case of UPD(14)mat, overexpression of maternal genes and non-expression of paternal genes explain the patient's phenotype (Ogata and Kagami, 2008; DHidalgo-Santos, 2018).

Phenotypic characteristics related to PWS were: Global developmental delay, learning disability, palpebral fissures, hypotonia, obesity, childhood eating problems, speech-articulation problems, and weak neonatal sucking and swallowing reflexes (Balbeur et al. 2016).

Among the other features are Camptodactyly, intellectual disability, mitral myxoid degeneration, abnormal collagen fibers, abnormal elastic fibers, weight gain between 1 and 6 years, hypercholesterolemia, joint hyperlaxity, hyperpigmentation, heart failure, slanted nose, small nose, bridge depressed/low nose, broad nasal bridge, and precocious puberty) (Balbeur et al. 2016).

Schaaf-Yang Syndrome

DHidalgo-Santos et al. (2018) and Enya et al. (2018) reported four patients with a mutation in the *MAGEL2* gene. Phenotypic characteristics related to PWS were: Delay in global development- 4, short stature- 1, weak or high-pitched childhood crying- 2, seizures- 1, cryptorchidism- 1, GH deficiency- 1, scoliosis- 1, strabismus- 1, palpebral fissures- 1, hypotonia- 4, small penis- 1, weak neonatal sucking and swallowing reflexes- 4 and gastroesophageal reflux- 1 (DHidalgo-Santos et al., 2018; Enya et al., 2018).

Other features include: intrahepatic portosystemic shunt findings- 1, asphyxia- 1, atrophy- 1, brain atrophy- 1, autism- 2, low urine specific gravity- 1, low development of language-1, camptodactyly- 3, coarse facial features- 1, tonic-clonic crisis- 1, decay- 1, thin fingers- 1, FSH deficiency- 2, LH deficiency- 2, testosterone deficiency- 1, neonatal depression- 1, cavo-caval intrahepatic shunt- 1, central diabetes insipidus- 1, round face/full cheeks- 1, respiratory failure- 3, cleft palate- 1, flattened philtrum- 1, hypernatremia- 1, hyperprolactinemia- 1, hypertelorism- 1, hyperthyroidism- 1, hypertonia- 1, pituitary hypoplasia- 1, pulmonary hypoplasia- 1, hyposthenuria- 1, hypothyroidism- 1, respiratory infection- 1, adrenal insufficiency- 1, micrognathia- 4, low ears- 1, arched/high/hugged palate- 1, pallor- 1, panhypopituitarism- 1,equinovarus feet- 1, clubfoot- 1, pneumonia- 2, polyuria- 1, broad nasal bridge- 1, depressed nasal root- 1, bushy eyebrows- 1, fetal distress- 1, sweating- 1, high and/or prominent forehead- 1 and volvulus- 1 DHidalgo-Santos et al., 2018; Enya et al.. 2018).

Chromosome 15q Deletion

Cao et al. (2017), Tan et al. (2020), and Zhang et al. (2021) described three patients with mutations in the SNURF and SNRPN genes. Phenotypic characteristics related to PWS were: Obstructive sleep apnea- 1, reduced fetal activity- 2, global developmental delay- 2, small-appearing mouth/thin upper lip- 1, downturned corners of the mouth- 1, weak or high-pitched childhood crying- 1, cryptorchidism- 1, learning disability- 2, behavioral disturbances- 1, hyperphagia- 1, hypotonia- 2, hypoventilation- 1, small hands- 1, obesity- 2, almond-shaped eyes- 1, speech-articulation problems- 2, psychosis- 1, weak neonatal sucking and swallowing reflexes- 2, obsessive-compulsive disorder- 1 (Cao et al., 2017; Tan et al.. 2020; Zhang et al., 2021).

Among the other characteristics are anxiety- 1, autism- 1, low respiratory effort- 1, short fingers- 1, thin fingers- 1, long fingers- 1, depression- 1, respiratory distress severe- 1, facial dysmorphia- 1, dyspnea- 1, epicanthus- 1, bitemporal narrowing- 1, fatigue- 1, weight gain between 1 and 6 years- 2, hypothyroidism- 1, infection respiratory distress- 1, lethargy- 1, intrauterine growth limitation/retardation- 2, poor response to external stimuli- 1, testicular malformation- 1, spaced nipples- 1, large nostrils- 1, flat nose- 1, pneumonia- 1, fetal distress- 1, and attention deficit disorder- 1 (Cao et al., 2017; Tan et al.. 2020; Zhang et al., 2021).

Duplication of 15q

Three patients had mutations involving the long arm of chromosome 15. Hoggart et al. (2009) reported cases of hexasomy and tetrasomy. Hood et al. reported cases of partial trisomy.

PWS-related phenotypic characteristics were: Global developmental delay- 3, downturned corners of the mouth- 1, seizures- 3, narrow bitemporal diameter- 1, learning disability- 1, behavioral disorders- 1, dolichocephaly- 1, palpebral fissures- 1, hyperphagia- 1, hypotonia- 3, high pain threshold- 1, obesity- 1, childhood eating problems- 2, speech-articulation problems- 2 and excoriation disorder- 1 (Hood e al., 1986; Hoggart et al.,2009).

Other features include: ventricular enlargement with interhemispheric fissures- 1, hyperextensible joints- 2, delayed absorption of cerebrospinal fluid in the superior sagittal sinus- 1, autism- 1, bronchitis- 1, seizures/epilepsy- 2, tonic-clonic crisis- 1, dacryostenosis- 1, thin fingers- 1, decreased density of the frontal and anterior temporal regions- 1, epicanthus- 2, esophoria- 1, spasms- 1, spasticity- 1, myopathic facial expression- 1, sylvian fissures- 1, hypsarrhythmia- 1, macrocephaly- 1, hyperextensible hands- 1, adductor metatarsal- 1, upturned nose- 1, conjugated gaze- 1, low ears- 2, unfolded helix ears- 1, posteriorly rotated ears- 1, otitis- 1, arched/high/crowded palate- 2, pneumonia- 1, depressed/low nasal bridge- 1, mental retardation 1, eye roll 1, joint stiffness 1, and prominent underlying cerebral sulcus- 1 (Hood e al., 1986; Hoggart et al.,2009).

Duplication of Xq

Monaghan et al. (1998) and Linhares et al. (2016) described two patients who presented with this alteration. Phenotypic characteristics related to PWS were: Delay in global development- 1, short stature- 1, downturned corners of the mouth- 1, weak or high-

pitched cry in infancy- 1, clinodactyly- 1, cryptorchidism- 1, behavioral disorders- 1, palpebral fissures- 1, hypotonia- 2, high pain threshold- 1, small hands- 1, myopia- 1, obesity- 1, small feet- 1, problems food-related behaviors- 1, speech-articulation problems- 1, weak neonatal sucking and swallowing reflexes- 1, thick, slimy saliva- 1, excoriation disorder- 2, obsessive-compulsive disorder- 1 (Monaghan et al., 1998; Linhares et al., 2016).

Among the other characteristics are underweight- 1, hyperextensible joints- 1, increased peak lactate- 1, poor language development- 1, short fingers- 1, intellectual disability- 2, depression- 1, dilated ventricles of the brain- 1, sleep disorder/difficulty sleeping- 1, lack of social interaction- 1, weight gain between 1 and 6 years- 1, genu varus- 1, gynecomastia- 1, inguinal hernia- 1, hypothyroidism- 1, prominent incisors- 1, urinary incontinence- 1, erythematous lesions- 1, asymmetrical breasts- 1, low ears- 1, large ears-1, arched/high/huddled palate- 2, pectus excavatum- 1, high blood pressure- 1 and ptosis- 1 (Monaghan et al., 1998; Linhares et al., 2016).

Fragile X Syndrome

De Vries et al. (1992), Schrader-Stumpel et al. (1994) and Stalker et al. (2003) described ten patients with a mutation in the *FMR-1* gene. Phenotypic characteristics related to PWS were dental crowding and malocclusion- 2, global developmental delay- 5, short stature- 1, cryptorchidism- 1, hyperphagia- 1, hypogonadism- 1, scrotal hypoplasia- 1, hypotonia- 1, small hands- 8, obesity- 9, small penis- 4, small feet- 7, and speech-articulation problems- 1 (De Vries et al., 1992; Schrader-Stumpel et al., 1994; Stalker et al.; 2003).

Other features include: Hyperextensible joints- 2, delayed puberty 3, stubby fingers- 3, short fingers- 2, short toes- 2, thin fingers- 1, round face/ full cheeks- 8, sagging- 1, hyperpigmentation- 6, midface hypoplasia- 1, large earlobes- 1, stocky hands- 5, large hands- 1, deep eyes- 1, ears with prominent helical root- 1, large ears- 1, arched/high/hugged palate- 1, hyperelastic skin- 1, sparse pubic hair- 1, flat feet- 1, large feet- 1, wide feet- 5, pneumonia- 1, depressed/low nasal bridge- 1, plantar creases- 1, abnormal insulin/glucose ratio- 1, reluctance to make eye contact- 1, mental retardation- 3, somatomedin C above average- 1, large testes- 2, small testes- 3, shyness- 1, hyperconvex nails- 1, small nails- 1 and deep nails- 1 (De Vries et al., 1992; Schrader-Stumpel et al., 1994; Stalker et al.; 2003).

Other genetic defects

Chromosomes 15q Microdeletion and 18q Microduplication

Dello Russo et al. (2016) described one patient who presented this alteration. Phenotypic characteristics related to PWS were: Delay in global development, short stature, learning difficulties, hyperphagia, small hands, and obesity. Among the other characteristics are Delayed puberty, intellectual disability, sleep disorder/difficulty sleeping, weight gain between 1 and 6 years, large feet, and short neck (Dello Russo et al., 2016).

Chromosomes Xq disomy and 3p deletion

Ben-Abdallah-Bouhjar et al. (2012) described one patient who presented this alteration. Phenotypic characteristics related to PWS were: Global developmental delay, short stature, small-appearing mouth/Thin upper lip, seizures, cryptorchidism, hypotonia, obesity, small penis, speech-articulation problems, and weak neonatal suck and swallow reflexes.

Among the other characteristics are Underweight, abnormal hypoplastic corpus callosum, facial dysmorphia, epicanthus, bitemporal narrowing, rounded face/full cheeks, short philtrum, respiratory infection, urinary tract infection, intrauterine growth limitations/retardation, microcephaly, thin nose, small nose, oligohydramnios, flattened ears, short neck, pointed/protruding chin, high and prominent forehead, and frequent vomiting (Ben-Abdallah-Bouhjar et al., 2012).

Chromosomes 6q and 10p duplication

Desch et al. (2015) described one patient who presented a phenotype that appears to be related to chromosome 6 euchromatin and not chromosome 10. Duplication of the 6q16.3q23.3 region may be a candidate locus of PWLS with the *TCBA1* gene as a candidate for mental retardation and the *BMIQ3* and *ENPP1* implicated in obesity susceptibility.

Phenotypic characteristics related to PWS were: Global developmental delay, short stature, GH deficiency, learning disability, small hands, small feet, and speech-articulation problems. Other characteristics include Overweight, delayed puberty, low IGF-I concentrations, respiratory infection, livedo, skin spots, and saturnism (Desch et al., 2015).

Obesity

Blackburn et al. (2020) described two patients who presented this alteration, having a variation in the *SIM1* gene. Phenotypic characteristics related to PWS were: obstructive sleep apnea- 1, short stature- 1, behavioral disorders- 1, hyperphagia- 1, obesity- 2, and speech-articulation problems- 1.

Among the other characteristics are anxiety- 1, arthrosis- 1, intellectual disability- 1, facial dysmorphia- 1, sleep disorder/difficulty sleeping- 1, lack of social interaction- 1, lack of O2 during labor- 1, hypercholesterolemia- 1, inability to focus eyes on objects- 1, macrocephaly- 1, low ears- 1, small ears- 1, Bell's palsy- 1, neck short- 1, cargo neck- 1, neurological problems- 1, and tremors- 1 (Blackburn et al., 2020).

TRAPPC9 (8q24)

Marangi et al. (2013) described two patients who presented this alteration, as having an alteration in the *TRAPPC9* gene. Phenotypic characteristics related to PWS were: Global developmental delay- 2, small-appearing mouth/thin upper lip- 1, downward-turning corners of the mouth- 2, clinodactyly- 1, behavioral disturbances- 1, hypotonia- 2, and speech-articulation problems- 2.

Among the other features are: anatomical brain changes- 2, brachycephaly- 2, seizures/epilepsy- 1, myoclonic seizures with hyperpyrexia- 1, hypoplastic supraorbital

ridges- 1, thin fingers- 1, intellectual disability- 2, sleep disturbance/difficulty sleeping- 2, epicanthus- 1, bitemporal narrowing- 1, round face/full cheeks- 2, weight gain between 1 and 6 years- 2, T2 hyperintensity- 1, hypertelorism- 2, hyperthyroidism- 1, raised earlobes- 1, thick ears- 2, placenta previa- 1, depressed/low nasal bridge- 1, wide nasal bridge- 2, synopsis- 2, straight and thin eyebrows- 2 (Marangi et al., 2013).

Mutation in exon 6 of the SNURF-SNRPN gene

Pellikaan et al. (2021) described one patient who presented this alteration. Phenotypic characteristics related to PWS were: obstructive sleep apnea, reduced fetal activity, global developmental delay, kyphosis, GH deficiency, diabetes mellitus (type 2), behavioral disorders, strabismus, palpebral fissures, hyperphagia, hypogonadism, hypotonia, hands small, obesity, almond-shaped eyes, small feet, food-related behavioral problems, speech-articulation problems, poor neonatal sucking and swallowing reflexes, and excoriation disorder (Pellikaan et al., 2021).

Other features include Primary amenorrhea, lack of pubic hair/few, cyanosis, thin fingers, vitamin D deficiency, dyslipidemia, bitemporal narrowing, weight gain between 1 and 6 years, low IGF, low hairline, wide nose, constipation, osteopenia, osteoporosis, bow feet, small chin, and trichotillomania (Pellikaan et al., 2021).

A summary of the most common clinical phenotypes entailed at the different loci described above that reflect genetic heterogeneity is presented in Figure 3.

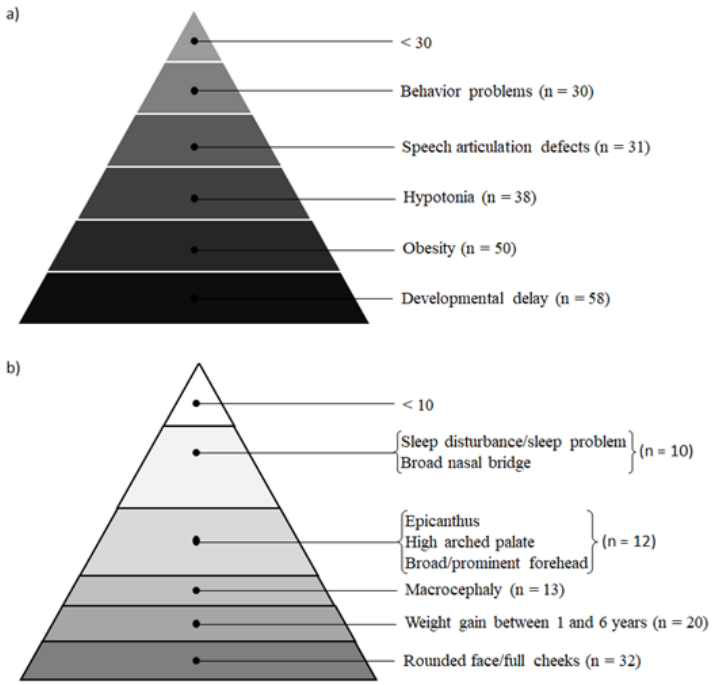

Figure 3. The most frequent phenotypic characteristics for Prader-Willi-Like Syndrome are described in the literature. a) Phenotype in common with Prader-Willi Syndrome (PWS) and b) Other characteristics found that are not classic of PWS. Diagram with the summary of the literature review search used.

The PWLS phenotype has been described in patients with chromosomal abnormalities 1p, 2p, 3p, 6q, and 9q, in cases with maternal uniparental disomy of chromosome 14 and fragile X syndrome (Berends et al., 1999; Faivre et al., 2002; Gilhuis et al., 2020). The most common clinical manifestations of PWLS include global developmental delay (78.4%), obesity (67.6%), hypotonia (51.3%), speech-articulation problems (41.9%), and behavioral disturbances. (40.5%).

DISCUSSION

Due to overlapping phenotypes, diagnosing patients with PWS is challenging (Candelo et al., 2018). Therefore, an alternative diagnosis must be sought. Because clinical diagnosis is difficult, these individuals are often not referred for treatment or misdiagnosed with PWS. This article can help facilitate this process. However, it is still necessary to understand how the metabolic pathways are affected differently in PWLS and PWS. Therefore, understanding the genotype-phenotype relationship in complex human diseases will be of great value.

The literature suggests that obesity and the PWLS syndrome are attributable to loss-of-function variants in the *SIM1* gene, included in the 6q16 region (Bonnefond et al., 2003). The *SIM1* gene encodes a transcription factor that acts on developing the hypothalamic paraventricular nucleus. Loss-of-function variants in *SIM1* may cause hyperphagic obesity with or without PWS-like features and, additionally, may be responsible for neurobehavioral disorders and short extremities (Bonnefond et al., 2013, Driscoll et al.,1998). Thus, *SIM1* haploinsufficiency may be responsible for severe obesity in some cases. Furthermore, deletions of *GRIK2* have been suggested to play a role in behavior disorders (Bonaglia et al., 2008). Observations have identified that the minimum critical region for PWLS is 1 Mb (Bonnefond et al., 2013). This region contains the *SIM1*, *MCHR2*, and *ASCC3* genes. Furthermore, *MCHR2* encoding a receptor for melanin-concentrating hormones increases mice's food intake and body weight. Therefore, as several genes with the 6q16 region are essential for controlling appetite and metabolism, a cumulative effect can cause the PWLS phenotype (Stein et al., 1996; Faivre et al., 2002; Rosenfeld et al., 2012; Desch et al., 2015).

Alterations in the epigenetic pattern may be associated with the variable expressivity observed in PWLS individuals. The phenotype may be due to the haploinsufficiency of paternally expressed genes located in the deleted region, as seen in the 6q16 region (Faivre, 2002 and Holder Jr, 2000). However, no evidence was found to associate an imprinting mechanism in the 6q16 region (Holder Jr, 2000; Spreiz et al., 2010).

Few cases were reported from Brazil and the rest of Latin America, and only two reported in the literature came from this region (Varela et al., 2006; Candelo et al., 2018). All other reported cases are from North America or Europe.

Analyzing the phenotypic overlap of PWS and PWLS, it is essential to understand the mechanisms that lead to the development of phenotypes. First, it is crucial to know the genomic regions and their role in phenotypic development. Genetic mechanisms are associated with a concept related to the cascade of relationships at different organizational levels from the initial ones, that is, the nucleotide sequence of genes, to the observable ones, characteristics of the organism. However, cause-and-effect links between traits are notoriously difficult to determine. Since these syndromes must share common affected

metabolic pathways, the understanding of the genotype-phenotype relationship remains to be clarified with the advancement of "Omics" science.

Understanding the genotype-phenotype relationship in PWLS can lead to new therapeutic approaches and impact genetic counseling. Up-to-date information on genomic regions, and the phenotypic characterization of individuals with PWLS is essential for a rapid diagnosis. In addition, the description of patients with PWLS benefits genetic screening. It improves the prognosis and quality of life of patients and family members who suffer from this disorder associated with obesity and hypotonia.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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